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**Granulomatous reaction to eyebrow permanent makeup successfully treated with
topical steroids in combination with topical tacrolimus**

Short title: Granulomatous reaction to EPMU

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Dear Editor:

Eyebrow permanent makeup (EPMU) is a cosmetic tattoo involving intradermal injection of colorants by piercing the skin with needles like in traditional tattoos [1,2]. Although EPMU can cause several adverse reactions similar to traditional tattoos, the risks are not fully known. Morales-Callaghan [3] reported that 3–8% of the general population has some type of traditional tattoo. Incel [4] reported that 2.1% of traditional tattoos have adverse reactions. EPMU, mistakenly considered as a cosmetic, has become increasingly popular, and the incidence rates of adverse reactions have not been established [1,2]. Frequent adverse reactions are local inflammation, infection, and allergic reactions [1-6]. EPMU contains black or brown colorants that were reported to be associated with systemic sarcoidosis [3,6]. EPMU can cause granulomatous reactions, which may be early manifestations of systemic sarcoidosis [3,4,6-8].

A 32-year-old Japanese woman presented with papules on her right eyebrow (Fig. 1A). She had a history of EPMU with no immediate complications, 4 years prior to the assessment. She had no history of keloids, atopic disorders, or allergies, or a remarkable family medical history. The histological examination revealed epithelioid granulomas in the dermis, with scattered brownish-black colorants and slight lymphocytic infiltrations (Fig. 1B-D). Ziehl-Neelsen immunohistochemical staining result was negative. Patch test results with the EPMU products were negative. Physical examinations, including chest radiography, electrocardiogram, laboratory tests (such as the angiotensin-converting enzyme), and eye examination revealed no abnormal findings. Based on clinical and histopathological findings, the skin lesions were diagnosed as a granulomatous reaction to the colorants. Some reports have suggested the efficacy of steroids, tacrolimus, allopurinol, and laser ablation [2,5,6]. Her symptoms were not

completely resolved with twice-daily use of a medium-potent topical steroid for 2 weeks. Serup [6] described the difficulty in predicting laser ablation outcomes because various colorants of tattoos have different absorption spectra and wavelengths. Moreover, EPMU treatment by laser ablation is difficult because of the remaining eyebrow hair. Therefore, twice-daily use of topical tacrolimus was administered, resulting in marked improvement 1 week later. Although the lesion recurred several weeks after the treatment was terminated, her symptoms had been completely suppressed by twice-daily use of a medium-potent topical steroid for 1 week, followed by twice-daily use of topical tacrolimus for 1 week, and concluded with the twice-weekly proactive use of topical tacrolimus. This sequential administration of topical steroids and topical tacrolimus was more beneficial than the administration of either agent alone.

Because EPMU can be performed outside the hospital, there are risks of infection or risk-management shortages. Although our case had negative Ziehl-Neelsen staining results, some cases infected by mycobacteria have been reported [1]. Wenzel [2] reported that several colorants have not been tested for use in EPMU and have caused adverse reactions. Ravits [9] categorized adverse reactions, and the symptoms seen in our case can be categorized as a foreign-body-like reaction. The colorants in and around the granulomas suggest this possibility, but should not be an exclusionary criterion for a diagnosis of systemic sarcoidosis because the foreign-body-like reaction on a tattoo can be its first sign of systemic sarcoidosis [3,4,6-8]. Ohtsuka [8] reviewed 12 Japanese cases of systemic sarcoidosis associated with traditional tattoos, and some reports recommended systemic work-up for patients with skin eruptions on tattoos [3,4,6-8]. No sign of systemic sarcoidosis was identified in our patient. Several reports, however,

have suggested that the time frame of sarcoidal reaction development may vary from days to years [2,3,7]. Thus, our patient should be followed up regularly. The removal of pathogenic colorants is difficult, and the persistence of colorants in the dermis may cause long-lasting recurrent adverse reactions, requiring continual treatments such as topical or oral steroids, tacrolimus, allopurinol, or laser ablation [2,5,6]. In our case, the symptoms have been suppressed by the sequential administration of topical steroids and topical tacrolimus, but the patient still needs continual treatment. Although no definite predictive tests have yet been utilized to estimate the individual risk of developing adverse reactions [2], patch tests and intracutaneous tests may have a predictive value [9]. In conclusion, we provide single-case evidence that treatment with topical steroids in combination with topical tacrolimus can be effective for EPMU, alerting consumers, beauticians, and clinicians about the possible risks of long-lasting adverse reactions to EPMU.

Sincerely,

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Nobuyuki Horita

Masanobu Sakaguchi

Masahiro Oka

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Conflict of interest: None.

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Figure Legend

Figure 1. Clinical appearance and histopathological examination

(A) Violaceous/brown firm papules are located on the right eyebrow, where the patient had eyebrow permanent makeup (arrows).

(B) Granulomatous reactions are revealed in the dermis, with abundant fine granular pigmentation (hematoxylin and eosin stain [HE]; original magnification: 40×).

(C), (D) Scattered brownish-black colorants (pigments) are present in and around some granuloma. (C, [HE]; 100×) (D, [HE]; 200×).

(E) Papules have been suppressed on proactive topical tacrolimus use.

